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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In Re Application of: M. Seul	)	
	)	Group Art Unit: 1641
Serial No. 10/645,426 Confirmation No. 8876	)	Examiner: Do, Pensee T.
Filed: 6/21/2003	)	
For: Arrays Formed of Encoded Beads Having Ligands Attached	)	

Commissioner for Patents
PO Box 1450
Alexandria VA 22313-1450

Reply To Supplemental Examiner's Answer

Dear Sir:

Please review the Supplemental Examiner's Answer in this matter in light of the comments below.

At the time of this writing, each party's arguments have been stated and re-hashed, and will not be repeated here except as necessary to further the understanding of the Margel and Singer et al. references, with respect to the Section 103(a) rejection of claims 76-84 and 86-90. The Examiner's argument, in essence, is that one would have been motivated to substitute the encoded spectrally-distinguishable microparticles of Singer et al. (which are conjugated to a ligand, the conjugate being free in solution but capable of binding to a target fixed to a substrate, thereby generating a bound microsphere complex) for the bound non-encoded microspheres in Margel, thereby generating an "array of several different [encoded] particle-attached ligands …said particles are encoded with a …characteristic that permits … *distinguishing of particles having different ligands attached thereto from each other* …" as in the instant claim 76.

Applicant's position is that a *prima facie* case is lacking here because, first, even if one combined Margel and Singer et al. as the Examiner advocates, one would not have the foregoing italicized element. Singer et al. is directed to:

> labeling or detecting one or more target materials using surface coated fluorescent microparticles with … an internal mixture of multiple fluorescent dyes. The mixture of dyes is a series of two or more fluorescent dyes having overlapping excitation and emission spectra allowing efficient energy transfer from the excitation wavelength of the first dye in the series, transfer through the dyes in the series and re-emitted as an optical signal at the emission wavelength of last dye in the series, resulting in a desired effective Stokes shift for the microparticle that is controlled through selection of appropriate dyes. {Abstract]

Multiple portions of Singer et al. make it clear that the intended use of the microparticles is to measure a collective signal, from a number of microparticles, indicating the presence of bound target – *i.e.*, distinguishing of different microparticles "*from each other*" is ***not*** intended and is not possible with the embodiments Singer et al. describe. First, it is noted that at col. 20, lines 33 et seq., Singer et al. describe spotting of nucleic acids on filter membranes to form the bound targets. Such spotting would *not* leave targets far enough apart to allow distinguishing different bound Singer et al. microparticles, as the spotting procedure provides a random target array, at unpredictable spacing, where many of the targets would be mere molecular-sized intervals apart. Moreover, at col. 17, lines 50-65 of Singer et al. state:

> several microparticle-labeled probes can be prepared where all the probes have the same excitation peak of the initial donor dye but each probe has a different emission peak detectably distinct from the emission peaks of the other probes. As a result, these microparticles are particularly suited for ***the simultaneous detection of multiple different target complements.*** Unlike radioactive methods, chemiluminescent labels or direct fluorophore conjugates, the subject microparticles can be made in a wide range of spectrally distinct colors that are simultaneously excitable with inexpensive, easily available equipment, such as hand-held uv lamps, and ***whose emission can be easily detected and distinguished by eye.***

At col. 14, lines 1-10, Singer et al. state:

> The microparticles can be manufactured in a variety of useful sizes and shapes, ***generally less than about 50 micrometers in diameter***. They may be spherical or irregular in shape. Typically, the labeled microparticles are between about 0.01 micrometers and about 50 micrometers in diameter and are spherical.

As the limits of resolution of the human eye are at about 100 microns (the thickness of a hair), it is clear from the foregoing paragraphs that the Singer et al. microparticles are *not* distinguished "from each other," as the eye cannot resolve particles of the size Singer et al. specify. The foregoing quotes clarify, therefore, that neither target nor microparticles are individually distinguishable in Singer et al., and only "smears" of fluorescent signals from the cumulative emission of multiple microparticle-labeled probes (which further prevent resolution of individual microparticles) are distinguished. This is also true in the Example relied on by the Examiner at col. 16, line 54 et seq. where in that assay, red fluorescence (not red ***microparticles***) is distinguished from green fluorescence (but not from green ***microparticles***).

Accordingly, even if Margel and Singer et al. are combined, at least one element of the claims is missing. Moreover, there is no motivation or suggestion to make such combination. Referring to the part of the Supplemental Examiner's Answer designated as Applicant's "Argument B" (page 8), Applicant wishes to add the following. Applicant has argued that the only relevant example of Margel is Example 31, relating to an immunoassay, but that there would not be any motivation or suggestion to combine this example with the microparticles in Singer et al., because the Example 31 microspheres all bear the same ligand (*i.e.*, are not and would not need to be "encoded") and are ***not*** on a planar substrate. The Examiner, however, notes that elsewhere, Margel describes a multiplicity of layers of microspheres, where the upper layers are covalently bonded to the lower layers with a ligand "B," and a different ligand "A" is used to bond the lower-most layer to the substrate (see col. 2, line 35 et seq.). The Examiner concludes "Thus, there are at least two different microspheres each having different ligands coated thereon."

But these A and B ligands are ***not*** ligands that one would want or need to distinguish – by attaching them to differently-encoded microparticles. These ligands are not intended to bind to a target, and would provide no useful information about a target if encoded and distinguishable (assuming that these microparticles were used in an assay). Accordingly, it is only Example 31 in Margel which is pertinent, and as the microsphere array in Example 31 is not even planar (*and* the microspheres are not encoded) there

clearly is no motivation or suggestion to combine it with the microparticles of Singer et al. This is a further reason that a *prima facie* case is lacking.

The remaining rejections, not addressed specifically herein (under Section 112, para. 2, and under Section 103(a) over the primary references in view of Nacamulli et al., for claim 85, and over the primary references in view of Gombinski, for claims 91 and 92) should be reversed for the reasons set forth in the Brief and the first Reply. In conclusion, reversal of all rejections is respectfully requested.

Respectfully Submitted,

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